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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/678,639	HE ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,32,36 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,32,36 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 31, 32, 36 and 37 are all the pending claims for this application.

2. Claim 31 was amended and Claim 34 was cancelled in the Response of 7/15/08.

3. Claims 31, 32, 36 and 37 are all the pending claims under examination.

4. Applicants amendments to the claims have necessitated new grounds for objection and rejection. This action is final.

Withdrawal of Rejections

Claim Rejections - 35 USC § 103

5. The rejection of Claims 31 and 37 under 35 U.S.C. 103(a) as being unpatentable over Song et al. (J. Biol. Chem. 275:23790-23797 (2000); cited in the PTO 892 form of 5/1/07) in view of Bui et al. (Biochem. Biophys. Res. Comm. 239:510-516 (1997); cited in the cited in the PTO 892 form of 5/1/07) is withdrawn.

The amendment of Claim 31 to recite that the agent used in the cancer cell growth inhibitory method is "a small interfering RNA (siRNA) complementary to all or a portion of a messenger RNA encoding said Dvl-3 protein" overcomes the rejection. Song in view of Bui teaches the use of the small molecule inhibitor, apigenin, to inhibit Dvl-3 expressing cancer cells in vitro.

6. The rejection of Claims 31 and 32 under 35 U.S.C. 103(a) as being unpatentable over Song et al. (J. Biol. Chem. 275:23790-23797 (2000); cited in the PTO 892 form of 5/1/07) in view of Bui et al. (Biochem. Biophys. Res. Comm. 239:510-516 (1997); cited

in the PTO 892 form of 5/1/07) further in view of Engelmann et al. (Phytomedicine 9(6):489-495 (2002) Abstract; cited in the PTO 892 form of 5/1/07) is withdrawn.

The amendment of Claim 31 to recite that the agent used in the cancer cell growth inhibitory method is "a small interfering RNA (siRNA) complementary to all or a portion of a messenger RNA encoding said Dvl-3 protein" overcomes the rejection. Song in view of Bui and Engelmann teaches the use of the small molecule inhibitor, apigenin, to inhibit Dvl-3 expressing cancer cells in vitro.

7. The rejection of Claims 31 and 36 under 35 U.S.C. 103(a) as being unpatentable over Song et al. (J. Biol. Chem. 275:23790-23797 (2000); cited in the PTO 892 form of 5/1/07) in view of Bui et al. (Biochem. Biophys. Res. Comm. 239:510-516 (1997); cited in the PTO 892 form of 5/1/07) and further in view of You et al. (Proc. Am. Assoc. Cancer Res. 42: 609 (2001); cited in the PTO 892 form of 5/1/07) as evidenced by Uematsu et al. (Oncogene 22:7218-7221 (2003); cited in the PTO 892 form of 5/1/07) is withdrawn.

The amendment of Claim 31 to recite that the agent used in the cancer cell growth inhibitory method is "a small interfering RNA (siRNA) complementary to all or a portion of a messenger RNA encoding said Dvl-3 protein" overcomes the rejection. Song in view of Bui and You as evidenced by Uematsu teaches the use of the small molecule inhibitor, apigenin, to inhibit Dvl-3 expressing cancer cells in vitro.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

8. The rejection of Claims 31, 32, 36 and 37 under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for using wnt or dvl-3 siRNA to inhibit dvl-3 expression in just any cancer in order to inhibit cancer cell growth much less in vivo, is maintained.

For purposes of review, the rejection was set forth in the Office Action of 1/17/08 as follows:

> "Nature of the Invention/Skill in the Art
> The interpretation of Claims 31, 32, 34, 36 and 37 is of record. The relative skill in the art required to practice the invention is a clinical oncologist with a background in treating oncogenic cancers with a variety of test agents including small interfering RNA.
> Disclosure in the Specification
> The specification teaches in Example 4 anti-Wnt antibody-induced apoptosis is associated with down-regulation of cytosolic dvl-3 levels and that apigenin downregulates expression levels; Wnt siRNA downregulates cytosolic dvl-3 levels (Example 9); apigenin destabilizes dvl-3 and reduces protein levels in mesothelioma cells (Example 10); suppression of NCI-H1703 (squamous cell lung cancer cell line) growth by the dvl-3 siRNA but no effect on A549 (squamous cell lung cancer cell line) and SW480 (a colon cancer cell line with aberrant activation in the Wnt signaling pathway due to APC mutation) by the dvl siRNA (Figure 9). The specification teaches that siRNA and apigenin both result in degradation of dvl-3. Thus, the specification discloses inhibiting two kinds of cancer cell lines, mesothelioma and squamous cell lung cancer cell line, with dvl-3 siRNA, and in the case of the A549 (squamous cell lung cancer cell line) was ineffective altogether. The specification does not support the broad scope of the claims for inhibiting any cancer cell growth whether in vitro or in vivo, where the cell is contacted with any agent that inhibits dvl-3 expression and which results in cancer cell growth inhibition.
> Field of Art/Undpredictability/Undue Experimentation
> With respect to the use of antisense molecules, at the time the instant invention was filed, the art recognized significant unpredictability to equate phenotypes derived from antisense technology with phenotypes derived from true loss-of-function methods. According to Stein (Stein, C.A., Pharmacology and Therapeutics 85: 231-236, 2000):
>
> > "[A]ntisense oligonucleotide biotechnology has entered a phase of its development in which many problems engendered by non-sequence specificity are being recognized and being actively addressed. However, in order to improve specificity of the methodology, attention must now also be aid to co-suppression of gene activity due to irrelevant cleavage." Stein further states that "[T]o the extent that this issue also is addressed, correlations between the down-regulation of a defined target and an observed biological outcome (e.g., growth suppression) *eventually* [*emphasis added*] may be possible." (page 235, Concluding remarks)

Stein clearly suggests that use of antisense oligonucleotide therapeutics are highly unpredictable due to "irrelevant cleavage" as a result of the low stringency requirements for RNAse H activity, wherein a 5-base complementary region of oligomer to target may be sufficient to elicit RNAse H activity (see Stein, abstract).

Stein also teaches (Stein, C.A., September, J. Clinical Investigation 108(5): 641-644, 2001) that:
"serious question have arisen as to whether an observed biological effect in an antisense experiment has indeed been produce by an antisense mechanism, or whether it is due to a complex combination of non-sequence specific effects. Investigators must therefore understand how to employ antisense technology properly and should recognize its limitations" (page 641, column 1, paragraph 2). However, in many, and perhaps most of the citations in which only a single oligomer was evaluated, the results reported may represent some combination of true antisense effects with sequence-nonspecific and cytotoxic effects" (page 642, column 1, lines 20-25). Except under rare and strongly justified circumstances, the use of an observed biological endpoint to claim antisense efficacy is not acceptable (page 642, column 2, lines 6-10).

Stein teaches several guidelines that reflect the state of the art at the time of filing of the instant application, including:

(a) that although computer-based approaches are being developed, it is still necessary to choose the optimal antisense oligonucleotide sequence from a panel of oligonucleotides, e.g. by mRNA "walking", (b) down-regulation of a relevant molecular target must be demonstrated, and (c) maximizing sequence specificity and minimize sequence non-specificity.

Stein teaches that only approximately one in eight (12.5%) of the putative antisense oligonucleotides tested can be shown to be active (page 642, column 1, lines 14-18). Other useful controls include:

(i) the use of two or more oligonucleotides of different sequences that are complementary to the same target. If the observed phenotype(s) are the same or distinct from those seen using control oligonucleotides, an antisense mechanism of target downregulation is strengthened, (ii) introduction of the target gene with one or more mutations in the region complementary to the antisense oligonucleotide. Lack of antisense inhibition in this case is suggestive, particularly if the antisense oligomer is still effective when the wildtype target is forcibly over-expressed (page 642, column 1, lines 40-65).

Caplen (Caplen, N.J., August, Gene Therapy 11(16): 1241-1248, 2004) addresses the degree of unpredictability in the art when choosing a biologically effective antisense sequence, stating that "it is unclear at this time (2004) what the minimum level of homology required between the siRNA and the target to decrease gene expression is, but it has been reported that matches of as few as 11 consecutive nucleotides can affect the RNA levels of a non-targeted transcript" (page 1245, column 2). This is especially relevant in mammalian cells because mammalian cells have nonspecific dsRNA-triggered responses primarily mediated through interferon-associated pathways that are absent in invertebrates and plants. While RNAi appears to be easy to induce, critical analysis of RNAi derived phenotypic data should not be overlooked. The validation of the RNAi effect in mammalian cells is important and that non-specific effects of RNAi need to be carefully assessed in mammalian cells (page 1245). For example, "ensuring the specificity and quantifying the efficacy of the particular siRNA or shRNA against a clinically relevant target transcript is essential in justifying its further development."

With regard to the ability of an artisan to correlate an observed antisense RNA phenotype to a predicted phenotype using targeting vectors that knock-out, gene disruption by selective ablation is the most definitive approach. Caplen teaches that the RNAi machinery can be saturated, so there will probably be a limit to the number of different genes that can be targeted in a cell at one time (page 1244, column 1). Furthermore, Caplen expresses the importance in recognizing that there is variation in the degree of inhibition mediated by different small interfering RNA sequences which may result in the production of different phenotypes. Thus, the disclosure of a phenotype in response to the expression of a single, structurally undefined antisense molecule (page 24, Example 4, Table 2, discussed below) cannot reasonably predict the phenotype obtained when the individual gene is totally disrupted.

Based on the disclosure of the specification and the prior art teachings for the general use of antisense molecules, the quantity of experimentation required to practice the invention as claimed would require 1) determining which of the infinite universe of antisense molecules could "target" any element in the Wnt signaling pathway that effects dvl-3 much less a dvl-3 siRNA or any one of the specific antisense molecules disclosed in the specification for dvl-3, 2) modes of delivery in a whole organism such that a single gene is inhibited and the desired secondary effect (treatment leading to the amelioration of conditions associated with the expression of a target protein in a patient) is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention. For example, the instant specification does not

appear to teach one of skill in the art which of the siRNA oligos can be used to effectively target cancer cells in vitro. Similarly, the instant application is not enabling for the use of the four oligo's *in vivo* in multicellular organisms, such as mammals, including humans."

Applicants' allegations on pp. 7-15 of the Response of 7/15/08 along with the enclosed references have been carefully considered and are not found persuasive. The examiner's response to the arguments appears in the order in which they are presented in the Response.

Under sections entitled "Inhibiting dvl-3 expression in any cancer" and "Treating a cell in vivo in a mammal" on pp. 6-7 of the Response, Applicants essentially summarize the rejection. These sections are addressed in detail below under the subheadings for "Legal Standard of Enablement" and "Enablement in Applicants' Specification is Commensurate with the Scope of the Claims."

a) "Legal Standard of Enablement"

Applicants allege "Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the *molecular biology arts [italics added]*. For example, in *Hybritech v. Monoclonal Antibodies, Inc.* the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments."

"Thus, in determining the scope of enablement, the Patent Office must consider the state of the art, including the knowledge available to the skilled artisan:

The scope of enablement.., is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation (*Invitrogen Corp. v. Clonetech Laboratories, Inc.)"*

Response to Arguments

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001). The invention requires that the skilled artisan make and identify siRNAs complementary to all or a portion of an mRNA encoding Dvl-3 protein without so much as any guidance in the specification as to how to proceed in generating and selecting the full genus of siRNAs. The skilled artisan is required to use by contacting a cell with any one of the genus of siRNAs to identify a reasonable number of species that effectively inhibit a Dvl-3-expressing cancer cell from growing whether this contacting is in vitro or in vivo. The method is not limited as to how the siRNA is administered to the cell, thus the ordinary artisan is required to determine the form in which siRNA should be presented or delivered for cell contacting as well as the growth-inhibitory effective amount that must be used in the contacting step to achieve growth inhibition. Applicants claimed invention is not only a chemical reaction or only a molecular biology art because each of these arts is an aspect of or a subcombination to the intended method art (method of using a gene therapy). Therefore in a determination of whether the total amount of experimentation required to practice the full scope of the method invention is undue, it is not apparent how the ordinary artisan can be guided by the cited case law in art fields that taken alone are not *on point*

to the instant method claim scope. For example, in *Hybritech v. Monoclonal Antibodies, Inc.,* the court discussed enablement in the context of the specification and known art teaching how (1) to make monoclonal antibodies; (2) to screen for proper monoclonal antibodies; and (3) to measure monoclonal antibody affinity. Further, in *Invitrogen Corp. v. Clonetech Laboratories, Inc.* the court discussed enablement in the context of the specification and known art for claims for cloned genes encoding reverse transcriptase lacking RNase H activity. Even though the claims described genetically engineered RT without regard to method used to mutate genes, and written description did not explain how to achieve claimed genes using point mutation, the claims at issue were not limited by the method of achieving the mutation, and the written description teaching regarding deletion mutation fully described operable method for achieving claimed mutation.

The facts regarding the instant method use of Dvl-3 siRNA are distinguishable from the cited case law. The specification teaches **making** siRNA at [0097] where: "The phenomenon of RNA interference is described and discussed, e.g., in Bass, Nature 411:428-29 (2001); Elbahir et al., Nature 411:494-98 (2001); and Fire et al., Nature 391:806-11 (1998), where methods of making interfering RNA also are discussed. The siRNA inhibitors are less than 100 base pairs, typically 30 bps or shorter, and are made by approaches known 30 in the art. Exemplary siRNAs according to the invention can have up to 29 bps, 25 bps, 22 bps, 21 bps, 20 bps, 15 bps, 10 bps, 5 bps or any integer thereabout or therebetween." The specification and the reference art of record do not teach making siRNA corresponding to all or a portion of the Dvl-3 mRNA. The specification teaches away from making a siRNA greater than 100 base pairs in length,

yet Applicants instant method requires a siRNA complementary to the *full length* Dvl-3 mRNA or any portion thereof that is indefinite in size. For example, the full length human Dvl-3 mRNA is 5062 bp (see attached NCBI NM_004423 deposit information), and the skilled artisan is required to determine where a siRNA should be complementary to "a portion" within this 5062 bp mRNA because the specification is specifically silent as to the number of species of siRNA for Dvl3 mRNA found to be operable.

The specification teaches **screening** siRNAs by example at [0168] "To further examine Dvl function, we synthesized small interfering RNA (siRNA) of Dvls that are capable of suppressing Dvl-1, -2, and -3. We tested the function of Dvl in the lung cancer cell line H1703 by treatment with Dvl siRNA and control siRNA. We chose H 1703 because it expresses Dvl-3 and has been shown to exhibit Tcf-dependent transcriptional activity of .beta.-catenin. After siRNA treatment, expression of dvl-3 was suppressed, while dvl-1 and -2 remained unexpressed. Of note, .beta.-catenin expression decreased accordingly in treated cells, which was accompanied by a significant reduction in Tcf-dependent transcriptional activity ($P<0.05$). Lastly, siRNA of Dvls inhibited H1703 cell growth in 24-well plates significantly ($P<0.05$) (FIG. 9). In addition, colony formation in 100-mm dishes was also suppressed significantly ($P<0.05$). In other cell lines with lower levels of Dvl expression compared to that in H1703, such as A549 (a lung cancer cell line) and SW480 (a colon cancer cell line with aberrant activation in the Wnt signaling pathway due to APC mutation), cell growth was unaffected by the Dvl siRNA." Thus the conclusion that can be drawn is that Dvl-3

siRNA inhibition of cell growth correlates with Dvl-3 protein expression levels in three cancer cell lines tested. Significantly, only a single example is shown where Dvl-3 siRNA is shown to inhibit cancer cell growth for a single type of cancer in vitro. Despite the working examples albeit limited in scope to three cancer cells lines in vitro, the specification does not teach the Dvl3 siRNA sequence much less the complementary region on the Dvl3 mRNA that was shown to be effective in targeting for cancer cell-growth inhibition in vitro. Thus the ordinary artisan could not even practice or reproduce the experiments disclosed in the specification absent regenerating and screening a plurality of siRNAs because the specification is silent regarding the actual Dvl3 siRNA used in any of the experiments.

And at [0172] the specification teaches "Furthermore, siRNA-mediated inhibition of Dvl expression in NSCLC cells decreased .beta.-catenin-mediated Tcf transcription, which further supports that Dvl overexpression is important to the canonical Wnt/B-catenin pathway in some lung cancer cells. Inhibition of Dvl also suppressed cell growth and colony formation in NSCLC cells, which indicates that aberrant upstream events in Wnt signaling is related to tumorigenesis in NSCLC." Notably and significantly, the specification does not even assist the ordinary artisan in explaining which Dvl protein (i.e., Dvl-1, Dvl-2 or Dvl-3) was examined for inhibition by siRNA technology in this experiment. Again, the ordinary artisan could not practice or reproduce this experiment without first having to generate and screen a plurality of siRNA for Dvl3 mRNA in order to proceed with the examination.

b) "Enablement in Applicants' Specification is Commensurate with the Scope of the Claims"

i) Applicants allege in the middle of p. 9 that advancements in the field of antisense oligo therapy have occurred since the publication date of the Stein article (cited in the previous Office Action) as evidenced by Sui et al. (PNAS 99(8):5515-5520 (April 15, 2002 (Exhibit A)) and Yu et al. (PNAS 99(9):5047-5052 (April 20, 2002) (Exhibit B)), and the method art is not highly unpredictable.

Response to Arguments

Initially, it is noted that neither Sui nor Yu describe oligonucleotide therapy occurring in any mammalian animal model much less a model for a relevant human disease correlate. Sui uses a DNA vector template from which a 21 nt siRNA is transcribed under the control of RNA pol III promoter in transfected cells in vitro to target gene expression for lamin A/C, cdk-2 or dnmt-1. Yu used an expression vector with a mouse U6 promoter to express 21 nt hairpin siRNAs and single-stranded siRNAs in vitro or in transfected cells to inhibit gene expression for GFP or neuronal β-tubulin. Both references envision gene therapy as a potential therapeutic endpoint, but the disclosures are strictly limited to demonstrating delivery of expression vectors in limited numbers of cells for a limited number of target mRNA sequences using 21 nt siRNAs.

These references taken alone are not any more enabling for using the siRNA technology beyond the limited in vitro-based cell assays disclosed in the specification. The references are not dispositive to Steins' teaching that oligonucleotide therapy is highly unpredictable irrespective of Steins's publication dates (2000 and 2001),

especially when the two references (Sui and Yu) are separated in time from Stein by approximately two years and are no further enabling for in vivo therapeutics than the instant specification. In response to applicant's argument based upon the age of the Stein reference, contentions that the references are old are not impressive absent a showing that the art tried and failed to solve the same problem notwithstanding its presumed knowledge of the references. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977).

ii) Applicants allege on pp. 9 to the top of 10 that the specification and working examples show the ordinary artisan how to design and use siRNA molecules "targeted to various regions of a Dvl-3 gene to inhibit production of the protein in vitro and in vivo"; the specification provides a working example (Example 11, p 49, lines 5-17) of an antisense oligo targeted to the processed Dvl-3 transcript.

Response to Arguments

The examiner fails to identify the written and enabling support for practicing the full breadth of the method claims in Applicants cited passage of Example 11, p 49, lines 5-17, which is incorporated by reference in full above. The examiner's same rebuttal arguments are applied here because only a single example for a given Dvl-3 expressing cancer cell line is shown to be growth inhibited by Dvl-3 siRNA in vitro. The specification does not even teach the Dvl3 siRNA sequence much less the complementary region on the Dvl3 mRNA that was shown to be effective in targeting for cancer cell-growth inhibition in vitro. Thus the ordinary artisan could not even practice or reproduce the experiments disclosed in the specification absent regenerating and screening a plurality

of siRNAs because the specification is silent regarding the actual Dvl3 siRNA used in any of the experiments in Example 11.

iii) Applicants allege on the middle of p. 10 the use of antisense oligos in animal models citing WO 2005/013901 (Exhibit C), particularly pp. 181-187.

Response to Arguments

This aspect of the response is ***incomplete*** because Applicants have provided only a copy of the cover page from the WO reference. Applicants are required to provide a full copy of any international reference under MPEP 609.04 (a). Applicants have not taken to time to explain how pp. 181-187 of the WO reference is analogous and relevant to the instant claimed method in order to meet their burden of proof in establishing enablement for siRNA technology in treating animal cancer models in vivo. See MPEP 716.07 "Once the examiner has established a prima facie case of lack of enablement, the burden falls on the applicant to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would have been able to make and use the claimed invention using the disclosure as a guide. *In re Brandstadter*, 484 F.2d 1395, 179 USPQ 286 (CCPA 1973)). ***Applicants are relying on the tactic of deluging the Office with numerous articles and references that have not been explained or properly considered by Applicants in their rebuttal arguments and comments.***

iv) Applicants allege "several antisense oligonucleotides were also known to be efficacious in humans and were advancing through clinical trials (see Exhibit D providing clinical trial records for NCT00017251, NCT00048295, NCT00048321,

NCT00078234, and NCT00056173)"; and "Also at the time of filing of the present application, it was known in the art that antisense oligonucleotides could be readily delivered to the liver (Bartshe et al., Pharm Res. 19(5):676-80 (2002) (Exhibit E))."

Response to Arguments

The Examiner respectfully requests that Applicants take the time to review their evidence proofs prior to submission in order to facilitate the examination process instead of filing a deluge of articles to effectively stymie the examination process.

For example, if Applicants took the time to review the clinical trial outcome for Genasense® (NCT00078234 (Exhibit D)), they would have known that the Genesense® clinical trial results were rejected by the FDA. See the attached MarketWatch report from March 18, 2008. This raises the question whether the other antisense clinical trial data from the reports enclosed under Exhibit D were approved or whether any conclusions have been made from those trials.

A brief search of the NEOPharm website (sponsor of the NCT00017251 trial) does not list LErafAON-ETU in the product pipeline. See attached pipeline profile for NEOPharm. Did the company drop the product or did the clinical trial fail? Clarification of this is requested of Applicants in order for them to sustain the position that any antisense therapy in vivo is enabled on the basis of the LErafAON-ETU clinical trial started in December of 2004.

A brief search of the MRC for the AVI-4658 PMO trial started October 2007 (NCT00159250) sponsored by the Imperial College of London indicates that the trial is active and the results are inconclusive. See attached report from the MRC. Notably,

Applicants do not even mention the NCT00159250 report in their comments but which is included under the "***bunch***" of clinical trial reports for Exhibit D.

A brief search for Pfizer's PF-00299804 drug trial starting October 2005 (NCT00225121) indicates that the trial is active and the results are inconclusive. Notably, Applicants do not even mention the NCT00225121 report in their comments but which is included under the "***bunch***" of clinical trial reports for Exhibit D.

A brief search for Aegera's XIAP antisense (AEG35156) trial (NCT00363974) started in October 2005 showed preliminary evidence of activity in lymphoma patients and that the drug was being advanced to dosing studies in July of 2008. See the attached Aegera report from July 31, 2008. Notably, Applicants do not even mention the NCT00363974 report in their comments but which is included under the "***bunch***" of clinical trial reports for Exhibit D.

A brief search for Isis' drug (ISIS 113715) trial (NCT00365781) started in August 2006 indicates that the trial is active and the results are inconclusive. See attached Isis pipeline product report. Notably, Applicants do not even mention the NCT00365781 report in their comments but which is included under the "***bunch***" of clinical trial reports for Exhibit D.

The examiner concludes from the "***bunch***" of clinical trial reports included under Exhibit D as filed, that only a single example of an antisense therapy (Aegera's XIAP antisense (AEG35156)) appears to hold any promise as an in vivo therapeutic in humans, but those clinical trials have not been completed.

Further, it is a frustration of purpose that Applicants refer to clinical trial reports for NCT00048295, NCT00048321, and NCT00056173 allegedly being included among the "***bunch***" of reports under Exhibit D as stated on p. 10, ¶3 of the Response of 7/15/08, when none of these reports are present. Should Applicants wish to pursue this line of argument during prosecution, they are required to provide the Office with copies of the clinical trial reports for NCT00048295, NCT00048321, and NCT00056173.

Finally, Bartshe has been considered for its disclosure that an antisense molecule could be taken up by the liver in an animal model. The extent to which this applies to human clinical trials in general and the treatment of cancer in vivo using a specific Dvl-3 siRNA is not made evident in Applicants rebuttal.

Applicants appear to have applied a literal meaning to the "preponderance of the evidence" standard used in assessing the enablement rejection by basing their rebuttal on the shear weight of paper filed in their Response.

v) Applicants allege that the delivery systems for administering siRNAs are enabled by the list of references cited in the table appearing on p. 11 of the Response and that the copies of the references are included with an IDS.

Response to Arguments

This aspect of the response is ***incomplete*** because an IDS with copies of the listed references does not appear to have been filed with the Response. Applicants are invited to verify the error by accessing the public PAIR system. Should Applicants choose to maintain this line of argument during prosecution, they are *required* to submit the IDS and references along with a *detailed explanation of the relevance* of all cited

references pertaining to how the references demonstrate enablement for using a DVl-3 siRNA in a method to inhibit growth of any cancer cell in vitro and in vivo. Upon submission of these materials, only then will the arguments be addressed.

vi) Applicants' allege the facts of the instant case parallel those in *Ex Parte Gleave* (Exhibit F). For purposes of brevity, the excerpted passages on pp. 11-13 of the Response of 7/15/08 are incorporated herein by reference.

Response to Arguments

The facts and basis of the enablement rejection in the instant case are not parallel to those in *Ex parte Gleave*. Applicants' specification: a) does not define the structure for a single example of an antisense Dvl-3 molecule. Applicants are welcome to show the complementary siRNA sequence(s) used in Example 11, for example, in the original specification as filed or the sequence listing as filed; and b) does not demonstrate a single example of an antisense Dvl-3 molecule that can delay progression of Dvl-3-expressing cancer cell growth in vivo in a cancer model.

vii) Applicants' allege the facts of the instant case parallel those in *Falkner v. Inglis* (Exhibit G) as evidenced by Gubser et al. (J. Gen. Virol. 85:105-117 (2004) (Exhibit H)). For purposes of brevity, the excerpted passages on p. 13 of the Response of 7/15/08 are incorporated herein by reference.

Response to Arguments

The facts and basis of the enablement rejection in the instant case are not parallel to those in *Falkner v. Inglis*. Applicants' specification: a) does not define the structure for a single example of an antisense Dvl-3 molecule much less the antisense

molecule that is required to be complementary to all or any portion of the Dvl-3 mRNA as instantly claimed. As discussed above, the specification teaches away from making a siRNA greater than 100 base pairs in length, yet Applicants instant method requires a siRNA complementary to the *full length* Dvl-3 mRNA or any portion thereof that is indefinite in size. For example, the full length human Dvl-3 mRNA is 5062 bp (see attached NCBI NM_004423 deposit information), and the skilled artisan is required to determine where a siRNA should be complementary to "a portion" within this 5062 bp mRNA because the specification is specifically silent as to the number of species of siRNA for Dvl3 mRNA found to be operable. Applicants are welcome to show the complementary siRNA sequence(s) used in Example 11, for example, in the original specification as filed or the sequence listing as filed; and Applicants' specification b) does not demonstrate a single example of an antisense Dvl-3 molecule meeting the structural requirements of the instant claims that can delay progression of Dvl-3-expressing cancer cell growth in vivo in a cancer model.

viii) Applicants' allege the facts of the instant case parallel those in *Falkner v. Inglis* (Exhibit I)). For purposes of brevity, the excerpted passages on p. 14 of the Response of 7/15/08 are incorporated herein by reference.

Response to Arguments

In *Invitrogen Corp. v. Clonetech Laboratories, Inc.* the court discussed enablement in the context of the specification and known art for claims for cloned genes encoding reverse transcriptase lacking RNase H activity. Even though the claims described genetically engineered RT without regard to method used to mutate genes,

and written description did not explain how to achieve claimed genes using point mutation, the claims at issue were not limited by the method of achieving the mutation, and the written description teaching regarding deletion mutation fully described operable method for achieving claimed mutation.

See the examiner's comments above under the section entitled "a) "Legal Standard of Enablement" which distinguish the facts of the instant case from *Invitrogen*.

The rejection is maintained.

New Grounds for Objection

Specification

9. The amendment filed 7/15/08 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicants have amended the specification to recite that the human Dvl-3 protein sequence corresponds to the sequence having accession no. "NP_004414". The original specification does not support this disclosure and Applicants have not provided any extrinsic evidence showing at the time of application filing that accession no. "NP_004414" actually provides the allegedly disclosed information. The provisional application nos. 60/491, 350 and 60/509,037 also do not provide written support the accession no. "NP_004414".

Applicant is required to cancel the new matter in the reply to this Office Action.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description/ New Matter

10. Claims 31, 32, 36 and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Newly amended Claims 31, 32, 36 and 37 are interpreted as being drawn to the limitation for “a small interfering RNA (siRNA) complementary to all or a portion of a messenger RNA encoding said Dvl-3 protein" as the cell growth inhibitory agent for the method invention.

The specification does not define a Dvl-3 siRNA as “a small interfering RNA (siRNA) complementary to all or a portion of a messenger RNA encoding said Dvl-3 protein". The specification does not provide literal or implied support for the limitation. The provisional application nos. 60/491,350 and 60/509,037 also do not support the limitation.

The specification defines a siRNA as discussed above under section 8 as "The siRNA inhibitors are less than 100 base pairs, typically 30 bps or shorter, and are made

by approaches known 30 in the art. Exemplary siRNAs according to the invention can have up to 29 bps, 25 bps, 22 bps, 21 bps, 20 bps, 15 bps, 10 bps, 5 bps or any integer thereabout or therebetween" (see [0097]). The provisional application no. 60/491, 350 provides the same definition for an siRNA at [0096] as the non-provisional application. The provisional application no. 60/509,037 does not provide a definition.

This is a new matter rejection.

Conclusion

11. No claims are allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

/David J Blanchard/
Primary Examiner, Art Unit 1643